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The Role of Atorvastatin in the Treatment of Chronic Obstructive Pulmonary Disease with Elevated High Sensitive C-Reactive Protein

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Abstract

Background There is a growing interest in the potential beneficial effects of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors drugs (statins) in chronic obstructive pulmonary disease (COPD) as anti-inflammatory agent. The basis of the systemic inflammation in COPD comes from two possibilities: spill-over effect or inherent systemic-based pro-inflammatory state conferred by a genetic disposition. The inhaler-based therapy for COPD aims to reduce symptoms, improve quality of life and reduce hospitalization, but does not substantially change disease progression or reduce mortality.

Objective To assess the efficacy and safety of statin therapy in COPD patients with evidence of inflammatory markers.

Methods Ninety patients were included in the study, aged 40 years or more, who visit the outpatient private clinic in Babylon government, Iraq from September 2012 to April 2016. They were divided randomly for 3 groups (receiving 40 mg, 10 mg atorvastatin or placebo, respectively), in addition to their baseline treatment. Severity reassessment performed after 6 months' duration of treatment as well as hospitalization frequency and mortality.

Results Statin therapy showed a significant improvement in the both doses treated groups regarding the HsCRP, CAT (chronic obstructive airway disease assessment test) score and forced expiratory volume in first second after 6 months of treatment. This improvement fails to be reported significant effect on CAT score when compared to placebo group. Thus, statin treatment doesn't show any symptomatic improvement as measured by CAT score over placebo treatment.

Conclusion The statin treatment in patient with chronic obstructive pulmonary disease can be useful in form of improvement of hospitalization, number of exacerbations but not mortality.

Keywords Atorvastatin, statins, COPD, high sensitive C-reactive protein.

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List of abbreviation: HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A, COPD = Chronic obstructive pulmonary disease, FEV1 = Forced expiratory volume in 1 second, CRP = C-reactive protein, HsCRP = High sensitivity C-reactive protein,

Introduction

Over the last 20 years, there has been a growing interest in the potential beneficial effects of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) in chronic obstructive pulmonary disease (COPD) [1-5].

The clinical studies suggest that statin therapy may confer a number of benefits in COPD such as reducing both the frequency of, and mortality from, infective exacerbations, reducing mortality from pneumonia, reduced decline in lung function and reduced risk of lung cancer [1,2,4]. While the benefits of statin therapy in COPD can be rationally explained by the known pharmacological effects of statins on the lungs [5,6] and justified where co-morbid cardiac disease commonly exists [1,7].

The basis of the systemic inflammation in COPD comes from two possibilities; either 'spill-over' effect from inflammation driven primarily in the lungs in response to aero-pollutants chiefly cigarette smoke exposure, neutrophilic inflammation and recurrent infection [8] or inherent systemic-based pro-inflammatory state conferred by a genetic disposition [1,9]. Smoking significantly enhances (possibly unmasking) this inflammatory disposition by being a recurring pro-inflammatory stimulus to the pulmonary and immune systems. This possibility is supported by data showing that poor lung function (reduced forced expiratory volume in 1 second (FEV1)), independent of smoking, predicts poor vascular and respiratory outcomes [10,11]. Conversely normal lung function, even after decades of smoking exposure, confers a greater 'degree of protection' from cardiorespiratory outcomes than that observed in those with poor lung function who have been lifelong non-smokers. These observations raise the possibility that systemic inflammation could be a secondary driver of inflammation in the bronchial epithelium alongside that derived from smoke exposure ('reverse' effect) [11,12].

Given that statins have been shown to lower systemic inflammation through inhibition of the inflammatory pathways mediated by NF-κB and IL-6 [13]. It is no surprise that statins are now considered effective anti-inflammatory agents, lowering systemic markers (IL-6 and C-reactive protein (CRP)) by over 50% in a matter of days [13,14]. It should not be forgotten that statins also possess important anti-apoptotic, anti-oxidant and anti-proliferative effects, whether these are independent of their anti-inflammatory effects is not known [14].

In the treatment of COPD, while currently recommended therapy for COPD is primarily inhaler-based, where the aim is to reduce symptoms, improve quality of life and reduce hospitalization, this approach does not substantially change disease progression or reduce mortality [15].

More importantly, these treatments do not improve the many and varied systemic manifestations of COPD. The only oral medication for COPD is roflumilast, which is limited to severe disease characterized by recurrent acute exacerbations of COPD [16,17].

This study is a clinical trial to assess the efficacy and safety of statin therapy in 2 different doses (high vs. low dose vs. placebo) for COPD patients with evidence of inflammatory markers as high sensitivity CRP (HsCRP) in term of severity, hospitalization and mortality.

Methods

Ninety patients from both genders were included in the study, whom age from 40 years and above. They were treated at the outpatient private clinic in Babylon government, Iraq, during the period from September 2012 to April 2016.

Inclusion criteria considered any patients with diagnosis of COPD by consistent history of smoking, clinical manifestation with spirometric criteria and high resolution computerized tomography (HRCT) findings who don't have any other diseases like ischemic heart disease, diabetes mellitus, hypertension or dyslipidemia neither before nor at time of diagnosis. For all enrolled patient, there is evidence of inflammation detected by positive HsCRP. All patients were in stable state maintained using inhaled budesonide /formeterol (160/4.5) twice daily and/or long acting anticholinergic and/or phyllocontine (225 mg) at night.

Those who are excluded from the trial included any patient refused the participation in the study or those with no obvious diagnosis of COPD or patients presenting during exacerbation episodes and patients not under regular treatment.

The 90 patients were divided equally and randomly into 3 groups:

Group 1: Thirty patients receive atorvastatin 40 mg at night

Group 2: Thirty patients receive atorvastatin 10 mg at night
Group 3: Thirty patients receive placebo treatment in addition to their baseline treatment for all 3 groups.
All patients are assessed at zero time for severity using chronic obstructive airway disease assessment test (CAT) score (clinical questions used to assess the control briefly by the patients word), spirometry in addition to their initial liver function tests, creatinine phosphokinase and HsCRP. A second assessment performed at 6 months' time for all the above initial evaluation as well as inquiring for COPD–induced hospitalization, exacerbations attacks and over-all mortality, in addition to adverse effect like myopathy or hepatitis picture necessitate medical seek. Primary end-points were reduction in HsCRP (inflammatory markers), FEV1 changes (physiological markers) and CAT score changes (clinical markers for diseases control). Secondary end-points were frequency of hospitalization, exacerbation and over-all mortality. Safety issues were also assessed like GIT effect, CNS effect as dizziness and amnesia, liver effect and myopathy.
Statistical analysis was carried out using SPSS version 17. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Mean ± SD). Paired t-test was used to compare means between paired numerical readings when difference between readings was normally distributed. Wilcoxon Signed Ranks Test was used to compare means between paired numerical readings when difference between readings was not normally distributed. A p-value of ≤ 0.05 was considered as significant.

Results

Patients' demography

As shown in table 1, the majority of patients were males and old age as the risk factor is smoking, which have a stronger effect in male and in elderly.

Table 1. The Distribution of patients with COPD according to age gender

Age (years)	Mean (64.52 ± 7.14)	Range (45-78)
Gender	**No.**	**%**
Male	51	56.7
Female	39	43.3
Total	90	100.0

Regarding frequency of hospital admissions in the 6 months of study; the majority of the patients does not need hospitalization as most of them could be treated as an outpatient as shown in (Figure 1).

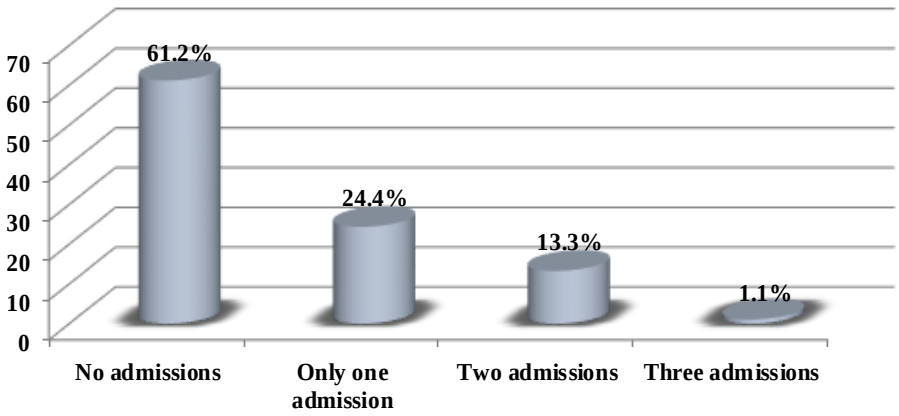

Figure 1. Distribution of patients according to frequency of hospital admissions

The distribution of patients with COPD according to frequency of exacerbations in the 6 months of the study is shown in (Figure 2) where the majority showed 1-2 attacks of exacerbation in a relatively short period, which represent the heavy burden of this disease on the health budget.

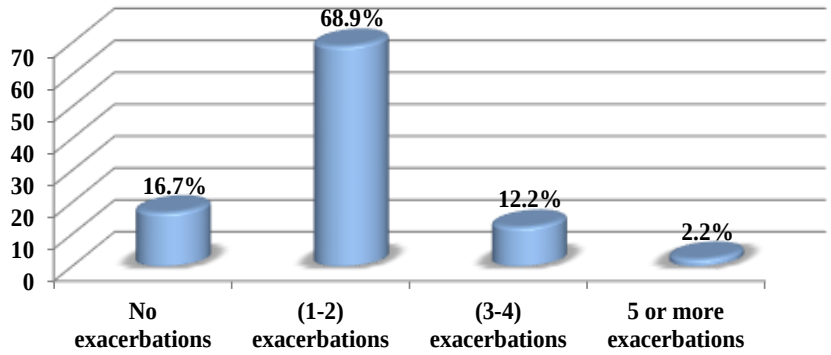

Figure 2. Distribution of patients according to frequency of exacerbations.

The distribution of patients with COPD according to side effects developed in the study duration: Both groups showed side effects, which mean that these effects may be not related to the drug treatment alone but also to the disease itself as shown in (Table 2).

Table 2. Distribution of patients according to side effects

Clinical side effects	Number	%
Nervous system		
Yes	28	31.1
No	62	68.9
Total	90	100
Liver abnormalities		
Yes	3	3.3
No	87	96.7
Total	90	100
Gastrointestinal system		
Yes	44	48.9
No	46	51.1
Total	90	100
Myopathy		
Yes	10	11.1
No	80	88.9
Total	90	100

Figure 3 shows the distribution of patients with COPD according to death in the study duration where death occurs in about (10%) of patients.

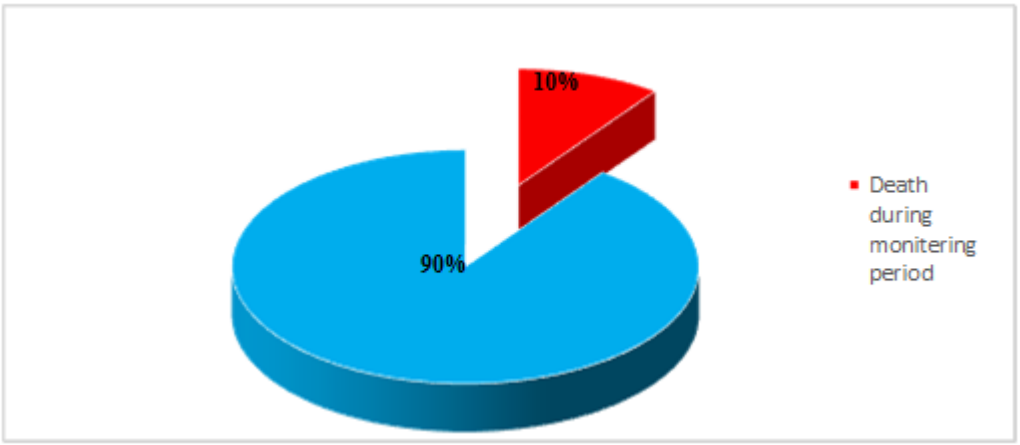

Figure 3. Distribution of patients according to death occurrence

The Study Groups and Study Variables analysis
There were no significant differences between means of age & gender in the three study groups as shown in (Tables 3 and Table 4) which indicate matching of the three groups.

Table 3. The mean differences of age by study groups

Gender	Group 1 No. (%)	Group 2 No. (%)	Group 3 No. (%)	P-value
Male	17 (56.7)	14 (46.7)	20 (66.7)	
Female	13 (43.3)	16 (53.3)	10 (33.3)	0.295
Total	30 (100)	30 (100)	30 (100)	

*p value ≤ 0.05 was significant
**p value ≤ 0.01 was highly significant

Table 4. The Distribution of patients with COPD according to age with each study groups

Study groups	No.	Age Mean ± SD	P value
Group 1	30	65.06 ± 6.52	
Group 2	30	65.23 ± 5.56	0.502
Group 3	30	63.26 ± 8.97	

Table 5 shows mean differences of HsCRP, CAT-score and FEV1 after treatment by study groups, there were significant differences between means of HsCRP and FEV1 by study groups, while there were no significant differences between means of CAT- score by study groups.

Table 5. Mean differences of CRP, CAT-score and FEV1 after treatment by study groups

Variable	Study groups	No.	Mean ± SD	P-value
CRP	Group 1	28	2.98 ± 1.05	<0.001*
	Group 2	28	3.32 ± 1.02	
	Group 3	25	4.57 ± 0.67	
CAT-score	Group 1	28	18.92 ± 5.44	0.53
	Group 2	28	17.60 ± 5.43	
	Group 3	25	18.96 ± 4.05	
FEV1	Group 1	28	47.96 ± 7.63	0.033*
	Group 2	28	47.57 ± 8.46	
	Group 3	25	42.76 ± 7.25	

Note: 9 patients from all groups died during follow up, *p value ≤ 0.05 was significant

The mean differences of HsCRP level, CAT-score and FEV1 before and after high dose of statin using (40 mg/day) is illustrated in table 6; were statistically significant.

Table 6: The mean differences of HsCRP, CAT-Score and FEV1 before and after high dose of statin

Variable	Categories	No.	Mean	P value
HsCRP	Before treatment	28	4.37 ± 0.94	< 0.001*
	After treatment	28	2.98 ± 1.05	
CAT-score	Before treatment	28	23.82 ± 5.38	< 0.001*
	After treatment	28	18.92 ± 5.44	
FEV1	Before treatment	28	38.28 ± 6.96	< 0.001*
	After treatment	28	47.96 ± 7.63	

Note: Two patients from this group died during follow up, *p value ≤ 0.05 was significant

The mean differences of CRP level, CAT-score and FEV1 before and after high dose of statin using (10 mg/day) is shown in table 7; were also statistically significant.

There was a statistically significant association between use of statin, frequency of hospital admissions and frequency of exacerbations among patients with chronic obstructive airway diseases as shown in table 8.

Regarding mortality, there was no significant association between use of statin and patient's mortality as shown in table 9.

There was significant association between use of statin and gastrointestinal upset and myopathy; while there was no significant association between use of statin and other system effects as shown in table 10.

Table 7. The mean differences of HsCRP, CAT-Score and FEV1 before and after low dose of statin

Variable	Categories	No.	Mean	P value
HsCRP	Before treatment	28	4.53 ± 0.84	< 0.001*
	After treatment	28	3.32 ± 1.02	
CAT-score	Before treatment	28	22.46 ± 5.29	< 0.001*
	After treatment	28	17.60 ± 5.43	
FEV1	Before treatment	28	39.35 ± 5.95	< 0.001*
	After treatment	28	47.57 ± 8.46	

Note: Two patients from this group died during follow up, *p value ≤ 0.05 was significant

Table 8. Association between patients' groups and frequency of exacerbation or hospital admissions

Study variables		Study Groups High dose No. (%)	Low dose No. (%)	Placebo No. (%)	P value
Number of admission	No	23 (76.7)	19 (63.3)	13 (43.3)	0.029*
	One or more	7 (23.3)	11 (36.7)	17 (56.7)	
Number of exacerbations	No	6 (20.0)	7 (23.3)	2 (6.7)	< 0.001*
	1 or 2	24 (80.0)	21 (70.0)	17 (56.6)	
	≥ 3	0 (0.0)	2 (6.7)	11 (36.7)	

*p value ≤ 0.05 was significant

Table 9. Association between study groups and mortality

	Study Groups High dose No. (%)	Low dose No. (%)	Placebo No. (%)	P-value
Dead during follow up	2 (6.7)	2 (6.7)	5 (16.7)	0.494
Still alive after follow up period	28 (93.3)	28 (93.3)	25 (83.3)	

*p value ≤ 0.05 was significant

Discussion

The majority of patients (61.2%) does not need hospitalization despite that 68.9% show single exacerbation, which means that much patients with mild COPD exacerbation can be treatment as outpatients, this finding is consistent with most of the clinical practice data [18]. Both the overall side effects seen in the study groups (statin or the placebo groups) are more in the GI upset and muscular effect, this was expected finding as the both can be induced by the drugs or the disease itself [19]. The overall mortality is 10% over 6 months, 5 patients of them in the placebo arm but the difference is not statistically significant, this finding is higher than Kirchmayer et al, which may be due to small sample size. The effect on all-cause mortality is a gray area because it is possible that there are potential beneficial effects of statins on cardiovascular comorbidities as it is known that smoking is a causative factor in the majority of patients with COPD and in the

development of coronary artery disease. Cardiovascular comorbidities are common in COPD patients [20].

Table 10. Association between study groups and side effects

Clinical manifestations	Study Groups			P value
	High dose No. (%)	Low dose No. (%)	Placebo No. (%)	
GIT upset				
Present	22 (73.3)	11 (36.7)	11 (36.7)	
Absent	8 (26.7)	19 (63.3)	19 (63.3)	0.005*
CNS				
Present	11 (36.7)	10 (33.3)	7 (23.3)	
Absent	19 (63.3)	20 (66.7)	23 (76.7)	0.510
Liver effects				
Present	3 (10.0)	0 (0.0)	0 (0.0)	
Absent	27 (90.0)	30 (100.0)	30 (100.0)	0.104
Myopathy				
Present	7 (23.3)	3 (10.0)	0 (0.0)	
Absent	23 (76.7)	27 (90.0)	30 (100.0)	0.015*

*p value ≤ 0.05 was significant

The finding from the current study that statins not reduced mortality in patients with COPD were inconsistent with most of the included studies [21,22]. However, a large multi-centre randomized clinical trial showed that statins had no effect on COPD exacerbations, which was consistent with this finding [23]. Several reasons might be accountable for this; only moderate-to-severe COPD patients were included in these studies and it is unclear whether statins were beneficial for patients with less impairment. In addition, the mean followed-up time was around 2 years, which might be a significantly different compared to the short-term effect in this study. Although the statin show a significant improvement in the both treated groups regarding the HsCRP, CAT score and FEV1 after 6 months of treatment, this improvement fail to show significant effect on CAT score when compared to placebo group i.e. the statin treatment not show symptomatic improvement measured by CAT score over placebo treatment. These findings consistent with some studies and inconsistent with others and that because it is depend on the study criteria and design as seen in Carlson et al study [24]. The statin treatment showed significant improvement of hospitalization, number of exacerbations but not mortality, again this finding is not proved yet [23,26]. The useful effect of statin was shown both in high and low dose in all primary endpoints but the side effects were higher in high dose arm as expected as the statin side effects are dose dependent [27].

In conclusion; atorvastatin use in COPD may have some beneficial effects on the disease profile mainly on the inflammatory aspects in addition to possible another useful effect on lung functions decline, frequency of exacerbations, hospitalization and even symptomatology of the patients. However, there is no clear benefits of statin in all-cause mortality outcome. The gastrointestinal and muscular adverse effects were significantly higher in the treatment groups patients.

It is recommended now to study the statin use in COPD in larger study with a longer duration and use other family drugs members and other doses to see whether it is group or drug related effects as well as using other inflammatory markers like interleukins (IL6) or tumor necrosis factor (TNF) to confirm their effect of the treatment in COPD.

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Conflict of interest

Drugs supplier and the payment for the drugs cost.

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